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AMERICAN JOURNAL OF PHARMACY

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Since 1825

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CONTENTS

MEMBERSHIP IN THE A. PH. A.

THE increase in dues for active members of the American Pharmaceutical Association to ten dollars per year should cause concern for no thoughtful member of the Association. Such a figure has been indicated for years both in view of the membership fee of similar scientific and professional organizations and on the basis of service rendered its members.

One of the chief weaknesses of American Pharmacy is the all too prevalent feeling on the part of its practitioners that industry, philanthropists or someone else should pay the full cost of the benefits that their own organization is able to derive for them. No other professional group is so minded. In fact, most scientists and professional people take pride in paying their own way and enjoy the feeling of well-being and independence that such a policy engenders. It has been aptly stated that a person appreciates fully only things for which he himself has paid. Is it not then possible that the increased membership fee may increase the appreciation and the respect that the members feel for their Association?

Insofar as the services of the A. Ph. A. are concerned, few if any organizations of a similar nature make a more determined effort to represent their members' interests and to do the hundreds of things that such a program entails. Progress in this direction has been particularly gratifying in the last few years and our professional recognition in other circles and with the government was never better. The full ramifications of the activities of our Association are appreciated by very few, for few indeed have or take the time to study them. We have on a number of occasions discussed before meetings of retail pharmacists the wide scope of work embraced in the A. Ph. A. and almost invariably a few conscience-stricken nonmembers request immediate membership. It is difficult for the A. Ph. A. officers themselves to do this much nedeed job for they are at once classified as being motivated entirely by self-interest. The acquisition of new members can be done much more easily by ordinary "run of the mill" members who believe sincerely in their Association and its service to pharmacy. Every member should accept this task as an individual and personal responsibility, for the growth of the A. Ph. A. in membership and strength fortifies one of Pharmacy's foremost bulwarks and directly benefits each of its members.

Retail pharmacists frequently are of the mistaken opinion that the American Pharmaceutical Association renders them little or no service whereas most agree that the National Association of Retail Druggists is a very worthwhile organization. The services rendered retailers by the N. A. R. D. are appreciated more because they are more direct and tangible. Pharmacists generally are ready to acknowledge the excellent work done by Secretary Dargavel and his associates in assisting the retail druggist in his complex problems. It should not be overlooked, however, that the thing which places the pharmacist apart from the ordinary businessman is his professional stature and this is maintained largely by the efforts of the A. Ph. A. Pharmacists should realize that their favored position as the purveyors of drugs and medicines stems from this professional recognition without which they would be in a sad position indeed. The retail pharmacist being both a business man and a professional worker must, if he is to maintain his present status, guard these professional qualifications just as zealously as he strives for reasonable profit for his business. It is surely true that were pharmacists to lose their professional recognition they would be thrown into a more highly competitive field where only a few would be able to continue on their present economic level. If for no other reason than this, every retail pharmacist should be a member of the A. Ph. A. for no other group is so constituted as to make the professional advancement and recognition of pharmacy possible.

Retail pharmacy alone is not the only area of pharmacy wherein increased membership is needed. Everyone who is a pharmacist or who derives his livelihood from pharmacy owes it at least his or her support by belonging to its parent organization. Colleges, wholesalers, manufacturers, etc., all should stress this point to their personnel and it should not require admonition from the A. Ph. A. officers to bring this about.

The A. Ph. A. is growing; it must continue to do so. The favorable effect on pharmacy that its growth is certain to have justifies an all out effort on the part of each member to drive home to each eligible non-member the obligation that he is shirking. The benefits that will result when the A. Ph. A. can speak with the authority of forty thousand members are real indeed. This is not an impossible figure but one that should and must be attained.

L. F. Tice

THE EGG INJECTION METHOD IN THE EVALUATION OF BACTERICIDES *

By Louis Gershenfeld and Bernard Witlin **

ADEQUATE criteria for the laboratory evaluation of antiseptics and bactericides, which are used under various conditions in practice, are lacking. The exact appraisal of such agents is a difficult task, inasmuch as no universal single laboratory (*in vitro* or *in vivo*) test is applicable under all conditions and for all compounds to be examined, even though the single test being used may make available more than one important characteristic demonstrating their usefulness. The limitations of any single laboratory test make it not only advisable but imperative to employ frequently an array of many different laboratory tests, so as to be assured that a proper evaluation is being made of the bactericidal efficiency of the material. One cannot help but conclude that a preparation revealing satisfactory findings by many different laboratory methods of testing, thus revealing a high rating in the overall picture, is useful in practice as an antiseptic or bactericide. In almost all instances, agents so tested and found constantly effective will meet the critical clinical evidence which must be the conclusive test in supporting the laboratory claims of efficiency.

The older laboratory tests employed for evaluating the efficiency of antiseptics were the widely-used U. S. Food and Drug Administration method (13) or modifications of this technique. Numerous controversial points have arisen concerning the use of these methods alone, especially when it is recognized that the F. D. A. procedure for water-soluble or water-miscible liquids is applicable only for phenolic compounds. It also is recognized that one must distinguish in these tests between bacteriostatic activity and a true bactericidal effect. This has resulted in either using a large volume of subculture medium or preferably incorporating inactivating agents in the subculture medium, as when using thioglycollate medium in testing mercurials or F. D. A. broth containing soap, oleates or lecithin when testing quaternary ammonium compounds.

* This investigation was conducted at the Philadelphia College of Pharmacy and Science, under a grant from the Iodine Educational Bureau's Industrial Fellowship at Mellon Institute.

** Presented at the 47th General Meeting of the Society of American Bacteriologists, May 13-16, 1947.

The F. D. A. method and preferably moidfications of it, which as laboratory tests will be more comparable or interpretable in terms of actual use in practice, will supply some worthwhile data concerning the effectiveness of the preparation upon bacteria. However, these tests do not supply information concerning the toxicity of the antiseptic or bactericide on living tissue. Many tests on living tissue have been proposed to facilitate the evaluation of antiseptics or bactericides as employed under practical conditions. Salle (1) and his associates have introduced the toxicity index, and in their *in vivo* test they note the highest dilution required to kill living embryonic chick heart tissue in ten minutes. Welch (2) and his associates also suggested determining the toxicity index of antiseptics, but for the observation of toxicity they noted the ability of the bactericide to destroy the phagocytic activity of leukocytes. The Nungester and Kempf technique (3) presents a direct *in vivo* procedure using a small portion of the tail of a mouse which has been immersed in a culture of the test organism and is then transplanted to the abdominal cavity of the same mouse. We employed a modification of Salle's technique and used it in the determination of the toxicity index of an antiseptic (4) (12). Sarbor (5), Lambert and Meyer (6), German (7), Buchsbaum and Bloom (8) and others have proposed various *in vivo* laboratory procedures. On the other hand, Price (9), Novak and Hall (10), Bost (11) and others present procedures for testing skin antiseptics in which the efficiency of the latter is determined on human subjects.

It is apparent that it is not always possible to obtain human subjects for toxicity tests. Even when it would be convenient for using such techniques, it would be best to employ other *in vivo* laboratory procedures as screening tests before employing as the final technique one in which the human subject is required. Many valid criticisms have been given indicating that the toxicity index of an antiseptic as determined by several of the available *in vivo* laboratory procedures are not of practical value, as the latter methods are too variable, too sensitive, expensive, difficult in performance or time consuming. Frequently, facilities are not at hand for properly carrying out some of the *in vivo* procedures advocated.

We therefore present a consideration of the egg injection method (4) as the *in vivo* laboratory test and the F. D. A. technique as the *in vitro* laboratory procedure for evaluating the toxicity of antiseptics

and bactericides for tissue as well as for bacteria. Theoretically, the greater the bactericidal properties and the lower the tissue toxicity, the better the bactericide for use in or upon the human body. This ratio of bactericidal efficiency to relative freedom from tissue toxicity is known as the "Toxicity Index" and is defined (4) as the ratio of the actual amount of the bactericidal agent contained in each cubic centimeter of the highest dilution required to kill Staphylococcus aureus in ten but not in five minutes at 37° C. (13), to the actual amount of the bactericidal agent required to kill a 9 day old chick-embryo within 24 hours.

$$\text{Toxicity Index} = \frac{\text{Actual amount of bactericidal agent in one cubic centimeter of the highest dilution killing Staphylococcus aureus in ten but not in five minutes at 37° C.}}{\text{Minimal amount of bactericidal agent killing 9 day old chick-embryo within 24 hours.}}$$

The minimal amount of bactericidal agent killing the 9 day old chick-embryo was determined by averaging the results of at least three different tests. The actual amount of germicidal agent present in the minimum lethal dose (M. L. D.) of the bactericide was calculated.

Experimental

A. Toxicity to Avian Embryo

Employing the technic previously described (4), 9 day old Leghorn chick-embryos were candled to assure vitality. The eggs were washed in soap and water, then allowed to stand for one hour in the incubator in a container holding a 1:1000 mercuric chloride solution. The shell area opposite the embryo was then swabbed with Strong Tincture of Iodine (7%) and allowed to dry for fifteen minutes. After the Strong Tincture of Iodine had dried, a small hole was drilled through the marked area to expose the membranae putaminis (the membrane lining the egg shell).

Using aseptic precautions, various dilutions of the bactericidal solutions made with sterile distilled water were rapidly injected into the egg through sterile ¼ inch, 27 gauge needles. The hole was then sealed with a drop of sterile paraffin at solidifying temperature.

The eggs were incubated at 38.5° C. in an oblique position, with the air sac up, turned twice daily and then examined for vitality by candling. Confirmation of vitality was made by opening the egg.*

The findings are recorded in the accompanying tables.

B. Bactericidal Efficiency Tests

The bactericidal solutions were tested by the Food and Drug Administration (F. D. A.) technic (13). The dilutions of bactericide capable of inhibiting the growth of Staphylococcus aureus in ten but not in five minutes were noted. All tubes revealing no growth were subcultured in flasks containing 100 cc. of F. D. A. broth to note bacteriostatic action.

Other tests as above were carried out with subcultures being made into thioglycollate broth instead of F. D. A. broth. This was employed because of the desirability of incorporating sulfhydryl-containing compounds in the subculture medium in testing mercurials (14) (15) (16) (17).

The findings are recorded in the accompanying tables.

It is of interest to point out that when tests were performed in accordance with the F. D. A. technique except that subcultures were made at minute intervals during a ten minute period, only in the case of the iodine solutions was the highest killing dilution the same at one minute as it was at the ten minute period.

Summary and Conclusions

1. The egg injection method as the *in vivo* laboratory test and the F. D. A. technique as the *in vitro* laboratory procedure were used and are suggested as satisfactory and more convenient procedures for evaluating the toxicity of antiseptics and bactericides for tissue as well as for bacteria.

2. Bactericidal efficiency tests were conducted using a group of commonly employed antiseptics and specific representatives of the halogens, mercurials, silver salts, phenolic and quaternary ammonium compounds. The Food and Drug Administration technique was employed using Staphylococcus aureus as the test organism. All

* Vitality is evidenced during candling by movement of the embryo and pulsation of the vitelline artery branches. When vitality is doubtful, eggs are opened and the embryo examined for heart beat.

TABLE I

Relative Toxicity of Bactericides to 9 Day-Old Chick-Embryos

F. D. A. Broth

Bactericide	Dilution of active ingredient killing S. aureus in 10 min. but not in 5 min. at 37° C.	A Concent. of active ingredient Gm/cc	9-day chick embryo MLD/cc of solutions (strengths as indicated under column "Bactericide")	B grams of active ingredient per MLD	$\frac{A}{B}=K$ Toxicity Index (K)
Phenol 1:20 aqueous	1:85	.01176	.12	.006	2.00
Hexylresorcinol 1:1000 glycerin aqueous soln.	1:8000	.00012	.16	.0016	0.8
Iodine (1:50 aqueous) soln. N. F. VIII	1:10,000	.000025	.1	.002	0.0125
Iodine 1:50 Tincture U. S. P. XIII	1:10,000	.000025	.07	.0014	0.18
Triethanolamine Hydroiodide 7.5% aqueous	1:150	.0065	1.5	.1125	0.058
Zephiran 1:1000 aqueous	1:35,000	.000037	1.0	.001	0.037
Zephiran 1:1000 tincture	1:35,000	.000037	.04	.00004	0.925
Mercuric Chloride 1:1000 aqueous	1:16,000	.00006	.02	.00002	3.00
Mercresin 1:500 tincture *	1:35,000	.000029	.02	.00002	1.45
Merthiolate 1:1000 aqueous	1:5000	.0002	.2	.0002	1.00
Merthiolate 1:1000 tincture	1:3000	.0003	.02	.00002	16.5
Metaphen 1:500 aqueous	1:3000	.0003	.15	.0003	1.00
Metaphen 1:200 tincture	1:1100	.0009	.014	.00007	13.00
Mercurochrome 1:50 aqueous	Did not kill	—	.04	.0008	—
Sodium Hypochlorite 1:20 aqueous	1:240	.00416	.04	.0004	10.4
Argyrol 1:20 aqueous	1:90	.011	.6	.03	.37
Cargentos 1:20 aqueous	1:100	.01	.9	.045	.22

* This is labeled 1:500, inasmuch as two active ingredients, each in concentrations of 0.1%, are present.

TABLE II

RELATIVE TOXICITY OF BACTERICIDES TO 9 DAY-OLD CHICK-EMBRYOS
THIOGLYCOLLATE BROTH

Bactericide	Dilution of active ingredient killing S. aureus in 10 min. but not in 5 min. at 37° C.	A Concent. of active ingredient Gm/cc	9-day chick embryo MLD/cc of solutions (strengths as indicated under column "Bactericide")	B grams of active ingredient per MLD	A / B = K Toxicity Index (K)
PHENOL 1:20 aqueous	1:85	.01176	.12	.006	2.00
HEXYLRESORCINOL 1:1000 glycerin aqueous soln.	1:8000	.00012	.16	.0016	0.8
IODINE (1:50 aqueous) soln. N. F. VIII	1:10,000	.000025	.1	.002	0.0125
IODINE 1:50 Tincture U. S. P. XIII	1:10,000	.000025	.07	.0014	0.18
TRIETHANOLAMINE HYDROIODIDE 7.5% aqueous	1:150	.0065	1.5	.1125	0.058
ZEPHIRAN 1:1000 aqueous	1:35,000	.000037	1.0	.001	0.037
ZEPHIRAN 1:1000 tincture	1:35,000	.000037	.04	.00004	0.925
MERCURIC CHLORIDE 1:1000 aqueous	1:8000	.00012	.02	.00002	6.00
MERCRESIN 1:500 tincture *	1:18,000	.000055	.02	.00002	2.75
MERTHIOLATE 1:1000 aqueous	Did not kill	—	.2	.0002	—
MERTHIOLATE 1:1000 tincture	1:4500	.00022	.02	.00002	1.1
METAPHEN 1:500 aqueous	Did not kill	—	.15	.0003	—
METAPHEN 1:200 tincture	1:1100	.0009	.014	.00007	12.85
MERCUROCHROME 1.50 aqueous	Did not kill	—	.04	.0008	—
SODIUM HYPOCHLORITE 1:20 aqueous	1:240	.00416	.04	.0004	10.4
ARGYROL 1:20 aqueous	1:90	.011	.6	.03	.37
CARGENTOS 1:20 aqueous	1:100	.01	.9	.045	.22

* This is labeled 1:500 inasmuch as two active ingredients, each in concentrations of 0.1%, are present.

dilutions of the bactericidal agents were subcultured into 100 cc. of F. D. A. medium to test for bacteriostasis.

3. Bactericidal efficiency tests were conducted in accordance with the Food and Drug Administration technic, but thioglycollate broth was used as the subculture medium.

4. Minimal lethal doses for 9 day old chick-embryos were obtained by the injection of the bactericidal solutions onto the chorio-allantoic membrane.

5. A number designated as the "Toxicity Index" was determined from a comparison of the bactericidal efficiency against Staphylococcus aureus, with the toxicity of the bactericide for chick-embroyos.

$$\text{Toxicity Index} = \frac{\text{Actual amount of bactericidal agent in one cubic centimeter of the highest dilution killing Staphylococcus aureus in ten but not in five minutes at 37° C.}}{\text{Minimal amount of bactericidal agent killing 9 day old chick-embryo within 24 hours.}}$$

6. The most favorable findings among the aqueous solutions of antiseptics were obtained with Iodine (aqueous 2% N. F. VIII). The toxicity index was 0.0125. Among the tinctures, Iodine Tincture 2% U. S. P. XIII revealed the lowest toxicity index, 0.18.

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SYNTHESIS OF METAL COMPOUNDS OF THE SULFONAMIDES BY ANHYDROUS REACTIONS *

By Simon L. Ruskin, M. D., and Mimosa Pfaltz, Ph. D.**

HIGHLY soluble salts of the sulfonamides have been extremely desirable, and, with the introduction of the sodium compounds, particularly sodium sulfathiazole, there were great expectations of an important advance in sulfonamide therapy.

Unfortunately, the pH of the sodium salt was so high that after the first wide application of the solutions, particularly the 5% solution, reports began to appear in the medical literature indicating that damage to the nasal mucosa occurred too frequently to permit of its general use. The ease with which sodium sulfathiazole sesquihydrate could be prepared also made it a very attractive compound for pharmaceutical use.

The calcium salts of the sulfonamides possess the great advantage of being much closer to neutral, having a pH between 8.2 and 8.5 which is within the range of physiological use, and yet being sufficiently soluble to make solutions up to 4%. However, an unfortunate characteristic of the calcium salt is a fairly rapid tendency to decomposition and precipitation. Another disadvantage of the calcium salts of the sulfonamides is the difficulty in preparation if made in water solution through calcium hydroxide because of the insolubility of both reagents. In preparing calcium compounds, we had slightly soluble calcium salts reacting with slightly soluble sulfa compounds producing end products soluble only to 4% and relatively unstable in solution. The reaction itself therefore necessitates large volumes of water, neutralization must be fairly exact, with resulting large volumes of the solution to be taken down in vacuo, all of this making factory production decidedly impractical.

It therefore became important to devise a method of preparation of the calcium salts that would be expedient in production and exact in result. This was accomplished by conducting the reaction in an anhydrous medium and by using preferably calcium methylate prepared freshly by reacting calcium metal in methyl alcohol.

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* Read before the American Chemical Society at a meeting at Cleveland, Ohio.

** Physiological Chemicals Co., New York, N. Y.

In hot alcohol, the sulfonamide compounds are fairly soluble, and if a slight excess of calcium methylate is added, the reaction proceeds promptly with a clearing up of the reaction mixture. The excess calcium methylate is filtered off, and the calcium sulfonamide salt is precipitated by cooling or adding excess chloroform with or without removing part of the alcohol.

Because of the fact that the reaction is conducted under anhydrous conditions, when precipitation by cooling is used, the alcohol can again be employed, thus providing a very economical procedure. By working in a neutral medium in alcohol with no hydroxyl ions present in solution, and with a temperature not going above 66° (the boiling point of the methyl alcohol) no hydrolysis of the sulfonamide linkage occurs, nor do we find decomposition. In this manner, the calcium salt is obtained in the pure state.

The next problem that presented itself in connection with the calcium salts was stabilization since the watery solutions of the calcium sulfonamides even after a few hours began to show signs of precipitation. This was a serious handicap to their usefulness since their increased solubility was primarily desirable for the preparation of solutions that could be applied to the mucous membranes.

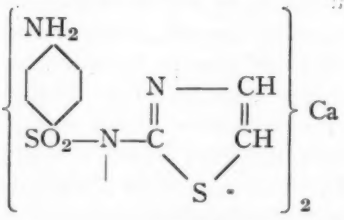
It was found that this could be overcome effectively by the addition of physiological amounts of calcium chloride; thus the addition of 0.033% of calcium chloride was sufficient to secure stabilization. The preparation of calcium sulfonamides by means of calcium metal was carried out as follows:

Preparation of Calcium Sulfathiazole with Calcium Metal

16 g. finely divided calcium metal (0.4 mole) were refluxed with approximately 500 cc. absolute methyl alcohol until all of the grey calcium metal had turned to white calcium methoxide. The resulting suspension was then treated with 135 g. (0.6 mole) sulfathiazole and warmed on the water bath until solution had practically taken place. The excess calcium methylate was then filtered off and the resulting solution concentrated to about 250 cc. At this point, it was a heavy syrup. The calcium sulfathiazole was precipitated by adding approximately 750 cc. chloroform with stirring. The product precipitated in an amorphous form, but crystallized rapidly

on heating a short time on the water bath. It was filtered after standing on ice over night. Yield 120 g. or 80%.

Reaction Products:



Analysis

Ca=8.44% found
8.26% theory

Preparation of Calcium Sulfapyridine

26 g. (0.1 mole) sulfapyridine were suspended in 200 cc. hot absolute methyl alcohol. To this was slowly added a suspension of freshly made calcium methylate which had been made by refluxing 2 g. (0.05 mole) calcium with 100 cc. absolute methyl alcohol. On heating the reaction mixture on the water bath, it began to clear up, but not completely. On the addition of 100 cc. more absolute methyl alcohol solution was complete. No precipitation took place on cooling. The reaction mixture was then concentrated at atmospheric pressure. To obtain a good yield, the reaction mixture was concentrated to a heavy syrup and then treated with excess chloroform. Yield 26 g. or 93%.

Preparation of Calcium Sulfanilamide

17.2 g. (0.1 mole) sulfanilamide were dissolved in 200 cc. boiling absolute methyl alcohol and treated with a suspension of freshly prepared calcium methylate made from 2 g. of calcium metal. Total volume of the reaction mixture was about 300 cc. It was boiled on the water bath for about one hour. At the end of this time the calcium methylate had completely disappeared with the formation of a flocculent precipitate of calcium sulfanilamide. After standing on ice over night, the calcium sulfanilamide was filtered off and washed with a little chloroform. Yield 12 g. or 63%.

Analysis

Ca 10.31% found
9.95% theory
S 16.01% found
16.70% theory

A second crop was obtained by addition of excess chloroform to the filtrate.

Working further with the anhydrous reaction, a most interesting development occurred. It was found that by means of calcium sulfonamide, the heavy metal salts including bismuth, arsenic, and antimony, as well as tin, iron and zinc could readily be produced. Unlike the sodium sulfonamides, which are insoluble in hot methyl alcohol, the calcium sulfonamides are readily soluble in hot methyl alcohol, so that the heavy metal chlorides dissolved in hot absolute methyl alcohol when added to a hot solution or suspension of the calcium sulfonamide compound react under boiling with precipitation of the heavy metal sulfonamide salts. The calcium chloride being soluble in methyl alcohol remains in solution. This latter fact is a further advantage over the use of sodium sulfonamides since while the calcium chloride is soluble in methyl alcohol, the sodium chloride is insoluble in hot absolute methyl alcohol. This method of preparing the metal sulfonamides by the anhydrous reaction through calcium sulfonamide provides a most expedient and practical method of production. The use of the anhydrous reaction also obviates the hydrolysis which is such a disturbing factor in the preparation of metal salts. The yields also are good as a rule, and are in some instances quantitative. As a typical example, antimony sulfathiazole was made as follows:

Preparation of Antimony Sulfathiazole

7.2 g. (0.03 mole) calcium sulfathiazole were dissolved in 25 cc. absolute methyl alcohol and treated under stirring with 4.6 g. (0.02 mole) antimony trichloride. The reaction began to take place immediately with the formation of a light pink precipitate. After stirring approximately one hour, the precipitate was filtered off and washed with a little absolute alcohol. Yield 7.7 g. or practically 100%. The product was insoluble in water.

Analysis	Sb.	15.16% found
		15.26% theory

Although the sodium sulfonamides are readily prepared in watery solution, the resultant compounds contain water of crystallization and unless the neutralization was quite exact, the pH of the sodium salt would likely be higher than the pure compound, and from the point of view of factory production would be less desirable. By using

the anhydrous reactions similar to that described for the calcium sulfonamides starting with sodium metal, an anhydrous sodium sulfonamide is produced free from hydroxyl ions of a pH that is consistently accurate and purer than the sodium sulfonamides prepared through the watery solution.

The procedure was as follows:

Preparation of Sodium Sulfanilamide

17.2 g. (0.1 mole) sulfanilamide were dissolved in 100 cc. boiling absolute alcohol. To this was slowly added, under stirring, 100 cc. of a solution of sodium methylate which was made by dissolving 2.3 g. (0.1 mole) sodium in 100 cc. absolute methyl alcohol. No crystallization took place on either heating or cooling. The reaction mixture was therefore concentrated to approximately 50 cc. and treated with an equal volume of chloroform. It was placed on ice over night and the product was then filtered off. Yield 15.5 g. or 80%. A second crop may be obtained by adding excess chloroform to the filtrate. The product was very soluble in water.

Na 11.44% found
11.85% theory

Preparation of Anhydrous Sodium Sulfathiazole

22.3 g. (0.1 mole) sulfathiazole was added to 100 cc. solution sodium methylate which was made by dissolving 2.3 g. (0.1 mole) sodium in 100 cc. absolute methyl alcohol. On shaking a few minutes, at room temperature, solution of the sulfathiazole was complete. On removal of approximately 80 cc. of methyl alcohol on the water bath, crystallization took place. The reaction mixture was then treated with excess chloroform and placed on ice over night. It was then filtered. Yield practically quantitative, 24 g.

Na 9.17% found
9.39% theory

Preparation of Sodium Sulfapyridine

26 g. (0.1 mole) sulfapyridine was added to 100 cc. solution of sodium methylate which had been made by dissolving 2.3 g. (0.1 mole) sodium in 100 cc. absolute methyl alcohol. On shaking a few

moments the entire reaction mixture crystallized to a solid cake. It was warmed a few moments on the water bath to complete the reaction and then treated with excess chloroform and placed on ice over night. It was then filtered off. Yield practically quantitative, 24 g.

Clinical Applications

The immediate practical results of this work have been that solutions of calcium sulfathiazole stabilized by calcium chloride to which a vasoconstrictor drug such as desoxyephedrine has been added provides a solution of sulfathiazole that can be used intranasally for the treatment of the acute cold and sinusitis without fear of necrosis or sloughing of the nasal membrane. The demand for such a preparation has been so great that, despite the known disadvantages of the alkalinity of the sodium compound, large amounts of the sodium compound are still being dispensed by leading pharmaceutical laboratories throughout the country. Attempts have been made to avoid the untoward reactions of the sodium compounds by using the poorly soluble suspensions of sulfathiazole combined with vasoconstrictors. For irrigation of the nasal sinuses, the simple calcium sulfathiazole solution shows none of the irritating effects observed with the sodium sulfathiazole, and therefore makes possible the use of 2 to 4% solutions of the sulfonamides in the treatment of sinusitis. The anhydrous reactions thus made possible the use of sulfonamides close to the physiological range required for human medication.

Conclusions

The synthesis of calcium sulfonamides by anhydrous reactions thus makes possible a series of pure calcium sulfonamides which are useful in the preparation of solutions for therapy. It also makes possible the preparation of a series of heavy metal salts of the sulfonamides by simple practical reactions.

THE PHYSIOLOGY OF CALCIUM, ITS CATALYTIC EFFECT ON THE MINERAL FACTOR IN NUTRITION.

By Armin Blumenthal, Ph. C.*

IN the last twenty years the research in the field of the physiology of calcium and its combinations in connection with organic life has brought many interesting results for nutrition and therapy.

Recent experience has shown clearly that the root of many diseases lies in diet deficiency, and that many serious conditions can be directly traced to the lack of calcium. This mineral deficiency, even when not serious enough to cause osteomalacia may affect bone structure in varying degrees. Nor are the effects confined to the bones, for while it has been estimated that over 90 per cent of the body's calcium is found in the bones and teeth, the remainder is, nevertheless, an essential element of the fluids and soft tissues of the body.

Coagulation of the blood could not occur, nor could the heart function normally, without the presence of sufficient quantities of ionized calcium in the bloodstream. Calcium vitally affects the functions associated with growth, reproduction and general health, including the secretion of the endocrine glands. (Holt, La Mer, Chown, Hoeber, Sherman, Peters and Van Slyke, Robinson and his collaborators, etc.).

In this article, mention of calcium is to be understood to refer to the different calcium compounds such as calcium oxide, calcium phosphate, calcium chloride, calcium gluconate, etc.

We know that the shells of snails and of many marine animals consist of calcium (mostly calcium carbonate), but it serves only as a protective cuticle; it therefore plays a passive part.

The physiologically active calcium in the chemistry of life is much more important; it is a potent factor in metabolism.

We know that the blood must have a certain percentage of calcium so that the functions of the heart may take a normal course, according to Ringer's theory. The clotting of the blood, the promotion of the phagocytosis and consequently the resistance against infectious

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diseases are determined by the quantity of calcium circulating in the blood. Calcium is necessary for the life-time of isolated organs, so that the period of their functioning may be increased.

The heart and other isolated organic parts preserve their contractility longer in a physiological solution containing calcium than in a solution of sodium chloride alone.

The same principle applies to the electric excitability of the nerves and the ciliae of the epithelium.

The eggs of certain animals do not develop, or only very abnormally, in water which does not contain any calcium.

This element is very essential for the skeleton and the bones to which it lends hardness and resistance, but it is at least just as important for the soft tissues.

The presence of calcium in the cell-nucleus leads to the following conclusions:—the cell suffers a drastic contraction by withdrawing from it the calcium-contents and finally dies away. The cell-nuclei, however, have to perform very important functions in the ganglionic cells, and therefore we are able to explain the very poisonous effect on the central nerve system caused by oxalates and fluorides. These elements combine with calcium, thus making it physiologically dead.

Calcium and magnesium are antagonists, counteracting in their functions. The magnesium salts undergo a high degree of hydrolytic dissociation, demonstrated by the phosphate of magnesium. Therefore we can conclude that the phosphate of magnesium supplies the phosphoric acid component used for the synthesis of cell albuminoids (nucleo-proteins and leucine).

The binding of phosphoric acid to calcium, sodium and potassium is too strong to make it possible for the cell to draw from these compounds phosphoric acid for the building of its vital ingredients.

Therefore the magnesium represents a cation acting as a transmitter of the phosphates which are necessary for the synthesis of vital organic cell substances.

A certain proportion of calcium and magnesium is indispensable for the maintenance of the normal vital functions of the cell.

A surplus of calcium causes a large formation of calcium phosphate which is very difficult to absorb and an intensive repression of the magnesium phosphates which can easily be split. Subsequently the phosphoric acid (one of the principal ingredients of nucleo-proteins and leucine) is too much anchored for being utilized.

When magnesium penetrates much more into the cells than calcium, the latter becomes restrained and the cell shrinks.

The danger to the respiratory-center caused by injections of magnesium sulphate is very well known. Meltzer and Auer of the Rockefeller Institute, New York, performed a very interesting experiment, demonstrating very strikingly the antagonism of calcium and magnesium. A subcutaneous injection of magnesium sulphate paralyzed conies completely; the paralysis disappeared instantly through a further injection of calcium chloride solution into the ear vein; the animal soon regained its strength and normal vitality.

According to the analysis of Katz and Jarisch the calcium-magnesium proportion of the blood is 1.4:1, a balance to be kept by a normal organism.

We find calcium in the organism in two different modifications: organic and circulating in the blood as bicarbonate. As we have seen, the latter is of special importance as a sort of protective calcium against both a surplus of magnesium and infectious diseases. The observation that whole cell-links become loose through lack of calcium (similar to the tearing asunder of algous threads) proves that calcium gives a certain density to the colloid structure of the cells.

The curdling of milk and subsequently the formation of cheese could not take place without calcium.

The organism absorbs calcium very slowly. It is secreted by the mucous membrane of the large intestine and in minute quantities by the kidneys.

Circulating calcium and organic calcium are always in a constant proportion. The restoration of the equilibrium which is sometimes disturbed occurs in the first place at the expense of the calcium in the bones. Then it affects the calcium reserve funds of the soft tissues, resulting in severe organic disorders such as nervousness, disposition to infectious diseases, tuberculosis, etc.

On the average the diet of cultured people does not comply with the calcium ration daily required by the organism. We know from statistics that *circa* 1 gram of calcium oxide would be necessary, but this quantity is never taken in the usual meat diet with potatoes and bread, unless these meals are supplemented by a great quantity of milk, cheese and vegetables.

Formerly our theory of nutrition was based on albumen, fat and carbohydrates; the mineral factor was completely neglected.

We pay more attention to it now than at any previous time, and mineral metabolism is now in the limelight of physiology.

Very often instinct leads to a proper diet, thus not endangering the calcium contents of the organism. So the Italian laborer adds to his daily ration of maize (lacking in calcium) cheese and fruit which are rich in calcium.

Nansen has observed that the Greenlanders, who are regarded as meat-eaters, long eagerly for vegetables and eat as a dainty bit the contents of the maw of killed reindeers; they eat also sea-weed with bacon. Scurvy, dermatosis, and tuberculosis are endemic diseases in Greenland. The Greenlanders do not enjoy long life.

In Brazil the meat diet predominates as well, because vegetables are very expensive in this country. This explains the low standard of health of its population.

Authorities on psychiatry have noted the existence of a relationship between calcium deficiency and mental diseases. It is obvious that the loss of calcium and phosphoric acid, very essential ingredients of the nerve cells, must have a deteriorating effect on the nerve functions and the intellectual sphere.

With regard to tuberculosis, statistics prove that lime and gypsum-burners are hardly affected by it. On the contrary general health conditions of workers suffering from tuberculosis improve in lime and gypsum mines. Lime dust appears on the affected tissue of the lungs as calcium carbonate, leading to a calcification and encystation of the tubercle-affected center.

Insufficient calcium retention reduces the alkalescence of the blood. The lower the degree of alkalinity of the blood, the more acid is the urine. Very often the acidity of the urine is a clear indication of abnormal calcium losses.

The physiology of calcium has been and will always be a problem for the pharmacist. Scientific research of the last twenty years has brought us great achievements, but great problems await still their final solution. May the pharmacist contribute his share.

The physiology of the vitamins is intimately connected with the calcium problem.

NEW MILLIONS FOR RESEARCH

By T. Swann Harding

WE live in an era of stupendous events which clamor for our attention. Many of these are spectacular, dramatic, and earth-shaking. No wonder we overlook in the news other events of fundamental importance, which would have drawn attention and excited great comment only a few years ago. One such is the passage and signing, August 14, 1946, of the Agricultural Research and Marketing Act, destined within 5 years to provide as much as 61 million dollars additional annually for research in the field of agriculture and marketing. Did you know about these new millions for research?

In terms of past authorizations for such expenditures this act is in every way remarkable. The Department of Agriculture itself started off in 1862 with annual appropriations in the neighborhood of sixty thousand dollars, only a small part of which was expended for research. Research in it has grown, of course, but this new grant tremendously strengthens the program.

The Hatch Act of 1887 authorized Federal grants of $15,000 a year to each State agricultural experiment station. The Adams Act of 1906 extended the original legislation, granted another $15,000 a year, and emphasized original research. No part of the funds it authorized were to be used for printing and only 5 per cent for land or buildings. The Purnell Act of 1925 granted a total of $60,000 to each State to pursue economic and social research, and permitted the expenditure of 10 per cent for buildings and land.

All of this might be called peanuts these days. But the Bankhead-Jones Law of 1935 provided for a Federal allotment of some millions for agricultural research, 60 per cent of which went to the State experiment stations, and 40 per cent to the Department of Agriculture. This was for research into laws and principles underlying the basic problems of agriculture in its broadest aspects.

Passage of this act, which germinated in the mind of Henry A. Wallace, marked a great advance. The act authorized the appropriation of a million dollars for the first fiscal year, and of a sum increasing by a million for each of the four years following, and of five

million annually thereafter. This money was appropriated for work in addition to research already provided for otherwise. Thus Congress itself recognized that fundamental research might often be more practical than research deliberately directed at the immediate solution of pressing problems.

Such research, for instance, proved that filtrable viruses could cause plant diseases. That one basic discovery furnished knowledge for the solution of many plant disease problems, all in one bundle. It extended beyond that to diseases of animals and of human beings. Similar fundamental research gave us our knowledge of the important roles played by vitamins and minerals in nutrition and in deficiency diseases, which again answered a horde of specific questions and solved a host of specific problems.

Fundamental research into the exact chemical composition of fats, carbohydrates, and proteins showed why certain substances served well as foods, and which were superior to which. The proteins, for instance, were broken down into what now number about twenty-four simpler compounds called amino acids, which are bound together in an infinite variety of ways to produce thousands of different proteins. Other problems loomed in the fields of long-range weather forecasting, elements present in soils in traces, the role of enzymes, the laws of genetics, photosynthesis—the process which enables green leaves to make starches and sugars in the sunlight, and so on.

Such research and many more projects have been pursued by Department scientists in nine especially established Bankhead-Jones regional research laboratories. The Agricultural Adjustment Act of 1938 added to this group of institutions the four Regional Research Laboratories built and equipped in Philadelphia, Peoria, San Francisco, and New Orleans, to use agricultural engineering to find new uses for farm products, surpluses, and by-products. They cost a million each; it requires a million more a year to operate each one, and their findings have already given the taxpayer a rich return on his investment.

Meanwhile the grants of Federal funds have enabled the agricultural experiment stations in each State to expand their activities and to work on valuable projects. Thus there has been built up a vast Federal-State network of research institutions, working in close collaboration on a wide variety of problems in the field of agriculture. The

Office of Experiment Stations, estabished in 1888, after passage of the Hatch Experiment Station Act, serves as a clearing house for projects and passes on Federal grants to the States.

The new Agricultural Research and Marketing Act of 1946 is, in part, an amendment to the Bankhead-Jones Act of 1935 mentioned above. Its function is "to provide for further research into basic laws and principles relating to agriculture, and to improve and facilitate the marketing and distribution of agricultural products." The act itself declares: "It is also the intent of Congress to assure agriculture a position in research equal to that of industry, which will aid in maintaining an equitable balance between agriculture and other sections of our economy."

Before discussing funds authorized for research, it should be said that the act has another rather unique provision. It provides funds for the *dissemination* of the results of this research, and that is something rather unusual, when so much opinion apparently holds that the Government should be secretive about its activities, and should not use radio, press, or other modern means of communication to give the public the facts.

The wise men who wrote the organic act founding the Department said that its function would be "to acquire and to *diffuse* among the people of the United States useful information on subjects connected with agriculture in the most general and comprehensive sense of that word." The act of 1946 reads that the Secretary shall "conduct and cooperate in consumer education for the more effective utilization and greater consumption of agricultural products." It also provides that, while none of the funds may be used to pay for newspaper, radio, or periodical advertising, the Department is to "collect and *disseminate* marketing information. . . . for the purpose of anticipating and meeting consumer requirements."

Too frequently this has been forgotten. Too frequently funds have been granted for the performance of research or of other investigations, but there has been great opposition to widespread publicity of the results. Yet Government is supported by the people, and there is a very fundamental reason for its efforts to use all modern channels of communication to dispense among those who support it the information and knowledge they paid to have created.

The new legislation ensures a much broader agricultural research program than ever before. It provides for the development of new

and the expansion of present uses for agricultural products, as well as for projects designed to improve marketing facilities and services.

More specifically, the research authorized will seek to discover, introduce, and breed new native and foreign agricultural crops, plants, and animals, with an eye especially to those that may be utilized in the chemical and manufacturing industries. Conservation of land, forest, and water resources for agricultural purposes; and the design, development, and more efficient use of farm homes, buildings, and machinery are all covered.

The funds will finance investigation of human nutrition and of the nutritive value of agricultural commodities, as well as of gains and losses in nutritive value which occur during the production, distribution, processing and home preparation of foods for consumer use. Effort will be made to discover new and extended markets for agricultural commodities and by-products, particularly of those likely to have periodic surpluses.

In performance of this research maximum use will be made of existing Federal-State facilities. The States and Territories and Puerto Rico will get payments ranging from 2.7 million dollars, to be appropriated in 1947, to 20 million in 1951, and for each year thereafter, for performance of this research. These funds must be matched by the State with their own funds.

Furthermore the act provides for additional research on present, new, and extended uses for agricultural commodities, products, and by-products, and there are to be appropriated for this sums ranging from 3 million dollars, in 1947, to 15 million in 1951 and each year thereafter, unless Congress deems it necessary to appropriate more. So far as possible this utilization research will be carried on in existing facilities, but the unusual provision is made that the Secretary may contract with public or private organizations to do the work if he sees fit.

Finally, the law advocates a scientific approach to marketing, transportation, and distribution problems similar to that which has been so successful in connection with the production of agricultural commodities. Moreover this field has been relatively neglected for many years. Take a few figures here with a swallow of water, or bourbon if you prefer.

Farm production accounts for only about 35 cents out of the dollar you spend for food products at your grocery store. Assembly

and transportation of these products absorbs 10 cents; processing takes 21 cents, wholesaling not quite 7 cents, and retailing nearly 24 cents. The majority of agricultural research has for years been concentrated on production, i. e., on that 35 cents. There is a point beyond which one cannot go here.

But how about research to cut down on that 24 cents of your dollar which the retailers get? The giant self-service markets opened new vistas here, though they didn't call what they were doing research. After all, wholesalers and retailers get over 30 cents out of the dollar you spend in the grocery, and processers get 21 cents. Considerable research, yet not enough, has been done on processing and considerable more on transporting agricultural products.

But it is that 30-cent item which should be attacked with especial vigor. Retailing alone represents about a fourth of the consumer's dollar for some items. The self-service supermarkets cut this cost largely by increasing the volume of operations per unit through new merchandising methods and by reducing the labor costs of retailing. Many other little efficiencies resulted, but there is still room for organized, wide-based research programs here.

There is room for tremendous improvement in marketing all up and down the line. No matter how effective work at the farm end of the marketing system, it can never produce great reduction in marketing costs, because only a small fraction of such costs is incurred near the farm. On the other hand, when a State experiment station recently demonstrated that rearrangement of machinery and labor operations could cut the direct labor costs of a cannery in half, that was progress.

Thousands of similar jobs, little and big, need to be done. The new law authorizes research on processing, preparing for market, packaging, handling, storing, and distributing agricultural products. It suggests studies to determine marketing costs in a way they have never before been appraised, to develop and improve quality standards, to develop plans for efficient marketing facilities, to improve transportation services and facilities, and to obtain equitable rates thereon, and to collect and disseminate marketing statistics.

Furthermore, the funds will be used to conduct studies and devise programs for eliminating artificial trade barriers, and to develop new and expanded markets and uses for farm products. They will finance consumer education and the collection and dissemination of

marketing information. They will finance the inspection, grading, and classification of agricultural products shipped in interstate commerce, and help develop and promulgate procurement standards and specifications for agricultural products.

The sum of 2.5 million dollars is authorized to conduct this research, in 1947, rising to 20 million by 1951. The annual appropriation thereafter will be 20 millions, unless Congress deems more to be necessary. From these funds the Secretary of Agriculture can make grants available to State departments of agriculture, bureaus of marketing, agricultural experiment stations, and such agencies, in amounts that they will match, for cooperative projects in the fields mentioned. In carrying out the projects the Secretary can cooperate with other branches of the Federal Government, with State agencies, or with private organizations.

The law provides for establishment of a national advisory committee, which has already been named by the Secretary of Agriculture, consisting of 11 members, 6 of whom must be producer representatives. Charles F. Kettering of General Motors and James G. Patton, president of Farmers' Union are two of the better known members. This committee will recommend research and service projects and assist in obtaining the cooperation between agencies and organizations needed. There are also twenty-one special committees to advise about research on particular agricultural commodities.

Today relatively little reliable information exists on costs, wastes, and weaknesses in marketing and distributing farm products. If the price spread is to be reduced, the entire process must be surveyed from farm to consumer, every step being closely examined. Since 1913 the farmer's share of the consumer's dollar has averaged only about 40 cents. Research should show how to reduce marketing costs so as to increase the farmer's profits.

Interstate trade restrictions, and both interstate and intrastate railroad, motor, and other rates require attention. There is pressing need for greater uniformity in State and Federal grading and packaging requirements. Every State has its own grading and labeling provisions. Special regions of the United States also have special problems which clamor for attention.

Passage of this new legislation marks a remarkable step forward for research. It opens tremendous possibilities. The adjective "stupendous" would not be inappropriate to describe it, in an era less filled

with daily events of large import. What a time we live in when so marvellous a program can be launched almost in secret, for few indeed are today aware that it exists, and these are mostly the individuals concerned with putting the enactment into effect.

Though no funds are yet available under the act, the Agricultural Appropriation Bill, as approved by the House of Representatives, provides funds of $9,500,000 to implement the research and marketing legislation. E. A. Meyer of the Office of the Secretary is Administrator of the Research and Marketing Act of 1946, and a recent secretarial order coordinated all Department of Agriculture research in the natural sciences under the Administrator of the Agricultural Research Administration, who had not previously had such direct relationship to investigations carried on by Forest Service and Soil Conservation Service. There matters stand at this writing. The Senate has yet to act on the Agricultural Appropriation Bill.

SELECTED ABSTRACTS

The Treatment of Acute Gold and Arsenic Poisoning: Use of BAL (2,3-Dimercaptopropanol, British Anti-Lewisite). A. Cohen, J. Goldman and A. W. Dubbs. J. A. M. A. *133*, 749 (1947). Toxic reactions in gold therapy are stated to occur in from 20 to 56 per cent of the cases treated. Unpublished observations based on a series of approximately 750 courses of gold injections administered by the authors include a number of toxic reactions such as generalized pruritis, seborrheic or exfoliative dermatitis, secondary anemia, agranulocytosis, jaundice, etc.

The authors report the successful treatment of 5 cases of acute poisoning due to gold and 1 case of acute poisoning due to arsenic by the intramuscular injection of a 10 per cent solution of BAL in peanut oil with 20 per cent of benzyl benzoate. The organic gold compound which had been used was "Solganal-B Oleosum" Schering (an oily suspension of aurothioglucose) in 4 cases, and "Lauron" Endo Products, Inc. (aurothioglycolanilide) in the other. The organic arsenical preparation was oxophenarsine hydrochloride.

In the majority of cases the initial dosage of the BAL solution was 2 cc. every 4 hours for 6 to 12 doses, after which the amount or frequency was reduced. BAL produced transient symptoms of toxicity including a sense of warmth in the mouth, salivation, flushing of the face, conjunctival injection, lacrimation and pains in the arms and legs.

It is suggested that the newer and less toxic BAL glucoside or other BAL derivatives for intravenous use may prove advantageous in permitting the more frequent use of gold compounds in the treatment of rheumatoid arthritis.

The authors consider that the mechanism by which BAL reverses the toxic effects of gold is identical with its action in poisoning by arsenic. It is believed that the latter reacts with the sulfhydryl groups of the protein fraction of cellular enzymes to form mercaptides. The sulfhydryl groups in the dithiol BAL compete effectively with these dithiol protein-metal compounds in the tissues, thus eliminating the heavy metal, relieving the biochemical lesion and restoring the enzyme system to normalcy.

The Treatment of Gold Dermatides: Use of BAL (2,3-Dimercaptopropanol). C. Ragan and R. H. Boots. *J. A. M. A. 133,* 752 (1947). Preliminary studies made on rats to which gold had been administered indicated that the subsequent treatment with BAL produced no toxic effects.

BAL was then used in the treatment of 5 patients with dermatitis due to gold. In all cases there was a definite increase in the urinary excretion of gold coincident with the administration of BAL. The dermatitis and pruritis disappeared in 4 cases and continued in 1.

In 4 patients there was an increase in the symptoms of rheumatoid arthritis within a month following treatment with BAL; in the fifth case, this therapy had been completed only two weeks before the paper was written. This observation suggests that the therapeutic effect of gold in the treatment of rheumatoid arthritis is a temporary suppression of certain processes which cause activity in this condition.

Bacitracin Therapy: The First Hundred Cases of Surgical Infections Treated Locally with the Antibiotic. F. L. Meleney and B. Johnson. *J. A. M. A. 133,* 675 (1947). The authors report that in the local treatment of a series of 100 cases of surgical infections with the antibiotic bacitracin, a favorable response was obtained in 88 per cent of the patients. The cases were unselected and comprised such localized or localizing infections as furuncles, carbuncles, ulcers, infected operative wounds, etc.

The properties of bacitracin were first described by the authors in 1945. An aerobic gram-positive spore-forming bacillus had been isolated from the debrided tissue removed from a compound fracture of the tibia; since the crude filtrate obtained from cultures of the organisms was found to possess a wide range of antibacterial activity, efforts to isolate the antibiotic principle were made. H. Anker, working in collaboration with the authors, obtained this substance as an amorphous, slightly yellowish powder by extracting the filtrate with butyl alcohol. The antibiotic received the name "bacitracin" in honor of the patient, Margaret Tracey.

The first 6 cases were treated with the crude filtrate, the next 30 with the partially purified product prepared by Anker, and the remaining 64 with material furnished by the Ben Venue Laboratories, where production on a larger scale had been studied. Bacitracin was

administered in two forms: (1) from 0.1 to 5 cc. of an aqueous solution containing 2 to 400 units per cc. as an injection into the center of the lesion, and (2) in a water-soluble ointment base. The latter was prepared by mixing 45 parts of Carbowax 4000 and 55 parts of propylene glycol, sterilizing by dry heat at 140° for 2 hours, and adding the bacitracin when the ointment had cooled almost to the point of solidification. The authors recommend 100 units of bacitracin per cc. of solution or gm. of ointment as an initial concentration.

In 31 cases the results were classified as "excellent," the criterion being a response within 72 hours. The results were considered questionable in 9 cases and as failures in 3.

Of the aerobic and anaerobic cocci found in these infections, 30 were resistant to penicillin but susceptible to bacitracin; 6 were resistant to bacitracin but susceptible to penicillin. None of the gram-negative aerobic bacilli that were tested were susceptible either to bacitracin or penicillin.

It was observed that bacitracin is not locally toxic or irritating and that it is not inhibited by plasma, blood, pus, tissues which have necrotic elements or a deficient blood supply, or organisms producing penicillinase.

Lipoid Pneumonia: A Pitfall in Diagnosis. R. E. Rewell. *Brit. Med. J.* No. 4499, 409 (1947). The author reviews the published reports on the changes produced in the lungs by the introduction of oils and adds a description of a fatal case of lipoid pneumonia which occurred in a healthy young woman. The fact that no history of the ingestion or aspiration of an oil by the patient could be obtained emphasizes the difficulties encountered in making the diagnosis in such a case.

This subject appears to have been studied first by Gueysse-Pellissier in 1920. This investigator injected olive oil into the trachea of the dog and the rabbit, finding it to be removed from the alveoli by phagocytes without leaving any trace. In 1925 Laughlen reported three cases with the lesions now known to be typical of lipoid pneumonia; two of these were infants who received liquid paraffin as nasal drops, and the other was a man with multiple paralyses who was taking this substance by mouth.

Since this time numerous reports on such cases have been published, all except one of which were observed in infants or in debilitated, aged, or paralyzed persons who were taking animal or mineral oil by mouth or as a nasal spray. The exception was an apparently healthy young woman who was taking cod-liver oil by mouth.

In 1928 Pinkerton described his experimental work on numerous oils in an attempt to find one suitable for use as a base for the introduction of radiopaque substances into the lungs. He found that vegetable oils produced no tissue reactions, being expectorated in a few days and leaving no trace. Animal oils were first emulsified and later attacked by phagocytes. Fibrosis occurred after two or three months, whether these oils remained in the lumina of the alveoli or reached the lymph nodes. Foreign body giant cells developed in both sites.

The irritating agents were the fatty acids liberated by hydrolysis, the extent of damage depending on the proportion of free fatty acids present in the oil and on the rate of hydrolysis.

Mineral oils produced an immediate phagocyte response in the alveoli and were rapidly emulsified. The droplets were transferred to the lymph nodes, but fibrous tissue reaction occurred far more slowly either in this site or in the alveoli than was the case with animal oils.

In the case reported by the author, the patient had an acute febrile illness resembling rheumatic fever with erythema nodosum. Clinical examination of the chest, cardiovascular system and abdomen revealed nothing abnormal, but from a radiograph of the chest a diagnosis of Hodgkin's disease was made. Two courses of deep therapy failed to produce marked changes in the enlarged mediastinal lymph nodes which were present.

Nearly ten months following the first admission to hospital the patient was readmitted in a dyspneic state. Radiograph showed increased mediastinal shadow and infiltrations near the lung roots. She died on the twelfth day thereafter. The findings at necropsy are presented; histological examination of the lung tissue revealed the changes characteristically caused by lipoid pneumonia. Inquiries made of the patient's family, employers, and medical attendants failed, however, to yield any history of contact with oil either as nasal drops, by mouth, or as a spray in connection with her work.

Effect of Organic Mercurial Preparations on Diseases of the Skin. E. A. J. Byrne. *Brit. Med. J.* No. 4489, 90 (1947). The author reports the treatment of 500 cases of skin lesions in the Tropics with phenylmercuric chloride (P. M. C.), acetate (P. M. A.), and benzoate (P. M. B.). Since P. M. A. and P. M. B. have a marked affinity for chlorine, it was felt that the change to P. M. C. would be rapid when applied, owing to the sodium chloride present in tissue fluid. For this reason P. M. C. was the compound preferred.

The literature on the bactericidal action of mercury compounds is reviewed briefly. The simpler the structure of the organo-mercurial, the more toxic it is toward all forms of life. The effect is determined largely by the character of the hydrocarbon radical; aliphatic mercurials are particularly toxic, whereas aromatic derivatives possess a relatively low local and systemic toxicity.

P. M. C. and P. M. A. were incorporated in three types of base: (1) in "eucerin" and distilled water, (2) in a preparation of the calamine lotion type, and (3) in solution in distilled water. The method of preparing each product is described. For the ointment a strength of 0.125 per cent of the organo-mercurial was found satisfactory. The lotion, which was applied to moist surface lesions, contained the following: P. M. C. 0.5 per cent precipitated on calamine, 15 gr.; zinc oxide, 30 gr.; glycerin, 30 minims; distilled water to make 1 fluidounce. For the treatment of large infected areas of deep-seated origin and for "jungle sores" a 1:8,000 aqueous solution was found to be effective.

No cases of sensitivity to organo-mercurials were observed. In some patients a slight and transient vesication was noted, chiefly around the spreading edges of the lesions. This condition disappeared within 24 to 48 hours, leaving a clean, healthy skin beneath. From the observations of previous investigators, coupled with the clinical results obtained in this series of cases, the author concludes that there appears to be no possible danger of toxic effects due to absorption of the organo-mercurial through the skin.

The Effect of d-Tubocurarine Chloride on Sensation in Man. J. H. Kellgren, A. J. McGowan and D. R. Wood. *Brit. Med. J.* No. 4484, 898 (1946). The authors review the published observations on the effect of curare preparations on the central nervous system, finding the experimental evidence confusing.

In order to investigate a possible analgesic action of *d*-tubocurarine chloride (Burroughs, Wellcome and Co.), the authors administered the drug in doses of 5 mg. and 7.5 mg., respectively, to two male subjects weighing 63.5 Kg. each. Sensation and cerebration were tested before injection, again in 5 minutes at the height of muscular weakness, and finally at 15 minutes after injection.

It was noted that the pain threshold was unaltered and that cerebration was unimpaired. In a later trial each subject received 11 mg. of morphine intravenously prior to receiving the curare preparation, which resulted in a definite rise in the pain threshold.

The author's conclude that in the doses administered *d*-tubocurarine chloride has no analgesic action, even at the height of muscular weakness.

Insecticidal Action of 1-Trichloro-2,2-Bis (p-Bromophenyl) Ethane (Colorado 9). G. M. List and M. G. Payne. *Science 105,* 182 (1947). A 5 per cent petroleum solution of Colorado 9 was found to kill flies within one hour at a concentration of 0.1 ml. of spray per cubic meter of air space. For tests of its effectiveness against the potato and tomato psyllid, the chemical was applied as a spray containing 1 pound per 100 gallons of water; a concentrate was first prepared by dissolving 1 pound of Colorado 9 in 1 quart of xylene and emulsifying 50 parts of this solution with 1 part of Triton 100 X. No indications of plant injury were observed from 5 applications of the spray. The yield of potatoes from treated plots was 313.2 bushels/acre, and only 22.8 bushels/acre from untreated plots.

Plot tests indicated that Colorado 9 offers promise in the control of tuber flea beetles and leaf hoppers. It was found to be lethal to the European elm scale.

No depressing effect upon the bacterial nodules of legumes resulted from the application of sprays containing high concentrations of Colorado 9, wherein it possesses a distinct advantage over DDT.

Synthetic Caffeine. C. C. Scott, E. B. Robbins and K. K. Chen. *Science 105,* 176 (1947). Ascertaining that the physical constants of a synthetic compound are identical with those of the natural product has been found to be no guarantee that the respective toxicities

are identical. It has been noted in the authors' laboratory that a sample of synthetic pyridoxine which conformed to N. N. R. specifications possessed much greater toxicity than the standard. As an extension of a previous study of synthetic alkyl derivatives of theobromine, the authors undertook a comparison of the pharmacological activity of totally synthetic caffeine with that of commercial caffeine prepared from a natural intermediate.

The extent of stimulation of the central nervous system was determined on rats, to which the respective samples were administered subcutaneously in a dose of 20 mg./Kg. Toxicity studies were carried out on mice; the LD_{50} of commercial caffeine by intravenous injection was found to be 79.36 ± 6.94 mg./Kg., and that of synthetic caffeine 75.51 ± 5.39 mg./Kg.

The authors conclude that synthetic caffeine and commercial caffeine possess the same degree of central stimulation and toxicity.

BOOK REVIEW

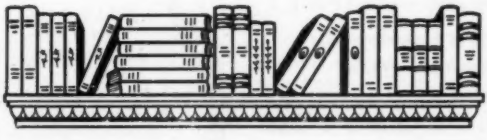
Natural Perfume Materials. By Y. R. Naves and G. Mazuyer. Translated by Edward Sagarin; xvii + 338 pages, including index. Reinhold Publishing Corp., 330 W. 42nd St., New York 18; 1947. Price: $6.75.

Few, if any, fields related to chemistry are more unknown than that of perfume materials, their source, production and characteristics. It is, therefore, a real event when one finds a book that deals authoritatively and in clear fashion with this great unknown. The authors, long associated with the field of perfumery, combine a chemist and a perfumer and thus embrace both the science and the art of this ancient calling. The translator has done a splendid job of putting into smooth and readable English the original text written, of course, in French.

The book is divided into four sections: Section I presents a brief history of natural perfume materials, Section II discusses modern processes of manufacture, Section III describes the chemical composition and analytical examination of the products of extraction, enfleurage and digestion, and Section IV lists monographs on natural perfumes.

The book is well worth its set price and every laboratory interested in perfume materials should have a copy. Those picking up the book for the first time will also find its contents and its style so interesting that much of it will be read for sheer enjoyment.

L. F. Tice



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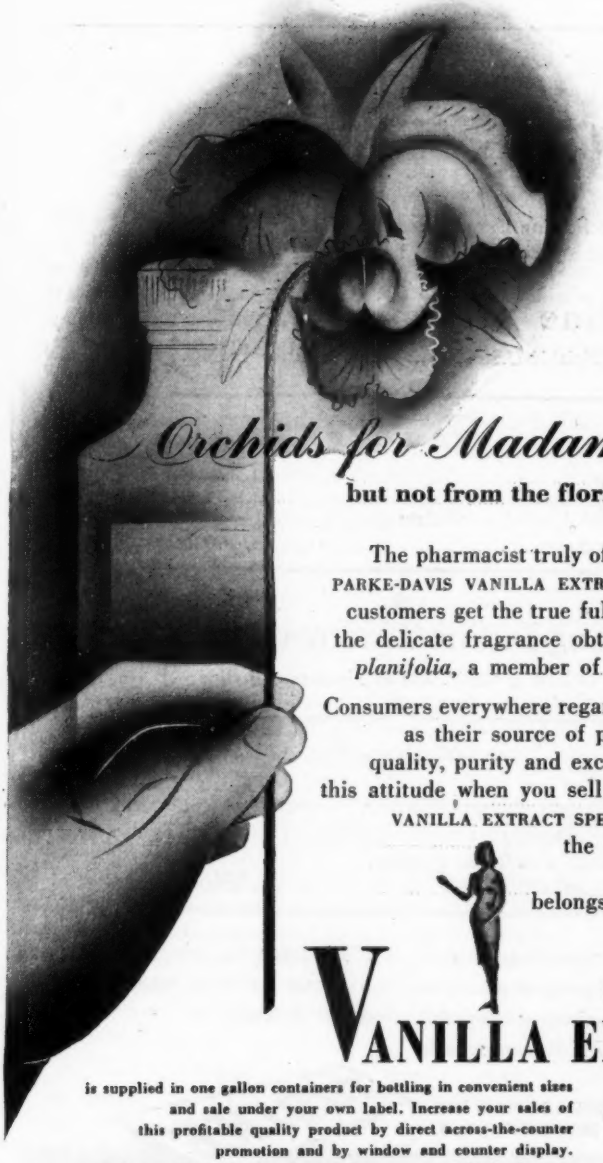

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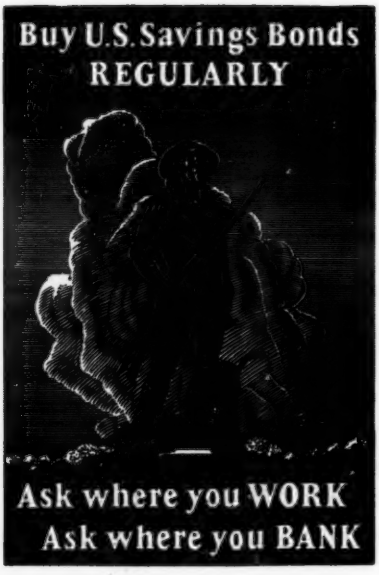
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